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Correspondence and Short Communications

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BRONCHOPULMONARY CARCINOIDS ASSOCIATED WITH CUSHING'S SYNDROME—REPORT OF A CASE AND AN OVERVIEW OF THE LITERATURE

In 1960 the first case of Cushing's syndrome caused by production of ectopic ACTH by bronchopulmonary carcinoids was published in Cancer (1). One year later the association of Cushing's syndrome and neoplastic disease had occurred with sufficient frequency to suggest a more than coincidental relationship (2). In 1963, the term 'ectopic adrenocorticotropin' for the production of ACTH by non-pituitary neoplasms was introduced (3). Reports of carcinoid tumors of the foregut secreting active substances, such as ACTH, 5-hydroxytryptophan, serotonin, histamine, and others, are scarce (4). Until now, 53 case reports of bronchopulmonary carcinoids with ectopic ACTH syndrome have been published (1, 5–43). We now present a case of Cushing's syndrome due to ectopic ACTH production by a carcinoid of the bronchus. A review of literature is also given.

Case report. In 1971, a 63-year-old woman was diagnosed as suffering from Cushing's syndrome and hyperpigmentation. Six months before admission symptoms started with the development of a moon face. Peri-renal airinsufflation showed enlargement of the left adrenal gland and a left-sided adrenalectomy was performed. Pathological examination revealed hyperplasia of the adrenal gland (wet weight: 14 g). However, after surgery the clinical and biochemical signs of hypercorticism persisted. At the second admission we saw a depressive woman with signs of hyperpigmentation of the skin, moonface and acne. Besides hirsutism, alopecia was present. She had a marked buffalo-hump and a severe muscle weakness was found. Bloodpressure measured 145/80 mm Hg. Routine laboratory examination showed no abnormalities. On the chest x-ray a rounded shadow in the left lung was found which had not been detected before. Radiographic examination of the lumbar spine was compatible with severe osteoporosis. Laboratory screening revealed a plasma cortisol level of 500 μg/l (normal 60–250 μg/l) and a plasma ACTH level above 2 μg/l (normal <0.1 μg/l). In urine the 17-ketosteroid level was 53 μmol/24 h (normal 14–52 μmol/24 h) and 17 hydroxysteroid level 44.5 μmol/24 h (normal 21–55 μmol/24h). Steroid output could not be stimulated by metyrapone or suppressed by dexamethasone. Serum vanillil mandelic acid (VMA), aldosterone levels and 5-hydroxyindoleacetic acid (5-HIAA) urine levels were normal. The patient was diagnosed as suffering from Cushing's syndrome due to ectopic ACTH production of a pulmonary tumor. At thoracotomy a yellow-brown tumor (diameter 2 cm) was found in the lingula of the left upper lobe. A segmental resection was performed. No lymph mode metatastases were present. Microscopic examination revealed two types of cells. Typical carcinoid cells were seen with uniform nuclei, which were negative when stained with Sudan black, argyrophillic, argentaffin and diazo stains. Electron microscopy revealed a few secretory granules in these cells. Also large cells with foamy cytoplasm were present. The histochemical reactions for Sudan black, for argyrophillic and argentaffin granules as well as diazo reaction were positive within these cells. Many secretory granules were demonstrated with the electron microscope. Immunofluorescence with anti-ACTH antiserum (Wellcome lot k 3102) was positive. The tumor contained 4.6 μg serotonin per gram wet weight. Postoperatively the hyperpigmentation and the Cushing habitus disappeared. Nineteen years after thoracotomy the woman was in good health without signs of ectopic ACTH production.

Review of literature. A total of 53 case reports on bronchial carcinoid in association with Cushing's syndrome have been described between 1960 and 1991 (1, 5–43). The data of a recent study are not included in the overview since individual data are lacking (44). The data of the 53 patients, 24 males and 29 females, were analyzed. The age ranged from 15–67 years (Table). In 42 cases the patient presented with symptoms related to the Cushing's syndrome as a moonface, a buffalo-hump, acne, hirsutism, striae, easy bruising, amennorrhoe, osteoporosis, hyperglycaemia and ankle edema. In 11 of these 42 cases, including our patient, a marked increase of skin pigmentation was also described (10, 11, 18, 19, 26, 28, 29, 41). In most cases the level of β-MSH (β-melanine stimulating hormone) was not measured. Seven patients presented with symptoms related to a tumor of the lung such as coughing, hemoptysis and increase of mucus production (5, 6, 14, 17, 21, 22, 24). In 2 cases flushing was the initial symptom (1, 34). In 3 cases additional flushing with increase of 5-HIAA urine levels was noted (6, 21, 35), and in another two cases flushing symptoms were reported without increase of 5-HIAA levels (1, 39). In all these cases metastases were present. Flushing was absent in one case although the 5-HIAA level in urine was elevated (14). No initial symptoms were mentioned in another two cases (11, 23). In 47 cases the tumor was classified as carcinoid tumor, bronchial adenoma of the carcinoid type, malignant bronchial adenoma, or as malignant carcinoid tumor. In 5 cases the tumor was called bronchial adenoma of the peripheral type (1, 9, 26, 41), as in one case there was no histological diagnosis (20). Tumor diameter varied from 1.0 to 7.0 cm (median 2.4 cm) (Table). In 14 cases lymph node metastases were found: in 7 cases metastatic spread was observed to regional lymph nodes (12, 18, 19, 27, 29, 35, 36) as in 6 cases lymph nodes at other sites (5, 6, 17, 19, 21, 32) were involved as well. In one case the site of lymph node metastasis was not mentioned (43). In 6 cases distant metastases were described (6, 8, 17, 19–21). Metastatic disease seemed not to be related to the size of the tumor.

Discussion. Review of literature revealed 53 case reports of which 37 patients underwent thoracotomy for surgical removal of a bronchopulmonary carcinoid tumor with etopic Cushing's syndrome. In only one-third of all the 53 cases the initial findings on the chest x-ray suggested a bronchial tumor. In 45% of these patients other surgical procedures have been performed. In 24 cases an adrenalectomy was done. In 3 cases only the initial chest x-ray showed the lesion (24, 28, 33). Better imaging techniques now obviate inadvert removal of the adrenals. Since the CT of the thorax and abdomen is available retroperitoneal airinsufflation has not been used anymore. In 12 of the 53 cases an additional

Table

Clinicopathologic findings in 53 patients with bronchopulmonary carcinoid tumors producing ACTH

Male/Female	24/29
Age—range	15–67 yrs
—median	45 yrs
Hyperpigmentation	n = 11
Tumor size	1.0–7.0 cm
Metastasized	n = 16

transsphenoidal exploration was reported. Again in three cases the initial chest x-ray showed a tumor as in one case CT-scan did (27, 36, 38, 43). Despite the availability of CT-scan the number of transsphenoidal operations did not decline. Of 10 carcinoid tumors found at autopsy 8 were not seen in chest radiographs, notwithstanding the fact that 3 of these tumors were larger than 3.0 cm (6, 9, 13, 16, 17, 19, 30, 37). When chest x-rays were repeated, 60% of the tumors became recognizable. At present the value of CT-scan in these cases is obvious (44). Another handicap in the diagnostic process was the fact that in only one-third of the reported cases the diagnosis ectopic ACTH syndrome could be confirmed biochemically. It can be stated that if the dexamethasone suppression test fails to induce a decrease of serum 17-OHCS, the patient has an adrenal cortical neoplasm with autonomous cortisol production or a non-pituitary neoplasm secreting ACTH. Cortisol producing tumors suppress the ACTH production of the pituitary gland so the plasma ACTH levels are normal. Non-pituitary tumors producing ACTH will of course lead to elevated serum ACTH levels. Cushing's syndrome can, however, also be secondary to ectopic production of corticotropin releasing factor (CRF) which interferes with the hypothalamic-pituitary axis. A minority of the tumors produce both hormones CRF and ACTH. Another problem is the possibility of periodic hormonogenesis of the tumor, a phenomenon which also has been observed in bronchial carcinoid tumors (17, 25, 36, 37, 39).

The treatment of choice for bronchial carcinoid with ectopic ACTH production is surgical removal of the tumor. Once the diagnosis bronchopulmonary tumor is made an anatomical resection of the involved lobe with lymph node resection should be performed. As a temporizing measure patients drugs are prescribed which suppress steroid production or which antagonize the glucocorticoid synthesis. Management of patients with long duration of Cushing's syndrome due to ectopic hormone production demands profound preoperative evaluation to trace the primary tumor. This includes CT-scan and MRI of head, thorax and abdomen to prevent unneccessary adrenalectomy or hypophysectomy.

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EFFECTS OF COMBINED TAMOXIFEN AND MEDROXYPROGESTERONE TREATMENT ON COAGULATION-FIBRINOLYTIC SYSTEMS IN PATIENTS WITH ADVANCED BREAST CANCER

It has been reported that tamoxifen (TAM) and medroxyprogesterone acetate (MPA) can cause significant changes in the clotting-fibrinolysis systems and thromboembolic complications (1–3). Combined TAM and MPA therapy is sometimes used in patients with advanced breast cancer. However, no studies have yet been reported concerning changes in the clotting-fibrinolysis systems caused by this combined hormone therapy. The combination of TAM and MPA might induce a state of hypercoagulation. However, a decrease of AT-III by TAM might be cancelled by a tendency of MPA to increase AT-III (1). In the present study, clotting and fibrinolysis-related hematological parameters were followed in a series of patients with advanced breast cancer treated by a combination of TAM and MPA.

Patients and Methods. Twelve postmenopausal patients with recurrent breast cancer receiving combined therapy with TAM and MPA in 1991 and 1992 were included in the study.

The patients were all postmenopausal; their age ranged from 46 to 79 years, with a median of 67 years. The disease free interval ranged from 6 to 180 months, with a median of 35 months. Five, 3 and 4 patients of them had metastasis to bones, lungs and locals, respectively, whereas none had liver metastasis.

TAM at 20 mg/day and MPA at 1 200 mg/day were orally administered simultaneously, and the following 10 parameters were analyzed before and 4 weeks after the start of treatment: alpha 2-plasmin inhibitor-plasmin complex (PIC; normal range <0.8 μg/ml; Teijin EIA kit), antithrombin III (AT III; normal range $<79-121\%$; COBAS BIO), D-dimer (Dd; normal range <150 ng/ml; ELISA (4)), fibrinogen (Fg; normal range 200–400 mg/dl; AUTO FI), plasminogen (Pg; normal range 75–125%; COBAS BIO), protein C (PC; normal range 70–150%; EIA (5)), thrombin-antithrombin III complex (TAT-III; normal range <0.3 ng/ml; EIA (6)), tissue plasminogen activator (t-PA; normal range <7.6 ng/ml; ELISA (7)), factor X (FX; normal range 56–138%; chromogenic substrate method (8)) and activated partial thromboplastin time (APTT; normal range 26–42 s; AUTO FI). The significance of differences between the mean values before and after treatment was analyzed by Student's t-test.

Results. The clinical results of the combined hormone therapy were classified as no change (NC) in all the patients, and none of

Table 1

Changes of hematologic parameters during treatment with TAM and MPA

Parameters (normal range)	Before treatment (median)	After 4 weeks of treatment (median)
PIC (<0.8 μg/ml)	0.69 ± 0.29 (0.70)	1.21 ± 0.94 (0.78)
AT-III (79–121%)	93.9 ± 21.5 (94)	100.4 ± 16.9 (100)
TAT-III (<3.0 ng/ml)	2.28 ± 0.75 (2.4)	5.22 ± 6.76 (2.8)
t-PA (<7.6 ng/ml)	3.12 ± 1.58 (3.3)	3.05 ± 0.93 (3.1)
Plasminogen (75–125%)	106.5 ± 14.6 (110)	106.0 ± 8.8 (107)
Fibrinogen (200–400 mg/dl)	251.0 ± 45.2 (250)	279.6 ± 47.4 (275)
Protein C (70–150%)	121.0 ± 15.5 (119)	107.0 ± 19.6 (106)
Factor X (56-138%)	114.0 ± 15.5 (120)	111.6 ± 13.4 (115)
D-dimer (<150 ng/ml)	126.1 ± 96.8 (148)	234.3 ± 328.1 (145)
APTT (26–42 sec)	27.7 ± 2.8 (26.8)	26.5 ± 2.6 (26.5)

(Data are shown as mean $\pm$ SD; NS)

Table 2

Changes of hematologic parameters in a 79-year-old patient with local recurrence of breast cancer

Parameters (normal range)	Before treatment	After 4 weeks of treatment
PIC (<0.8 μg/ml)	0.7	3.6
AT-III (79–121%)	86	93
TAT-III (<3.0 ng/ml)	3.8	23.0
t-PA (<7.6 ng/ml)	4.0	3.2
Plasminogen (75–125%)	96	121
Fibrinogen (200–400 mg/dl)	236	283
Protein C (70–150%)	113	113
Factor X (56–138%)	112	123
D-dimer (<150 ng/ml)	316	1077
APTT (26–42 sec)	27.5	25.8

them had significant change of the clinical condition. None of the 10 analyzed parameters was significantly changed by the treatment (Table 1). The mean values of 3 parameters (PIC, TAT-III and Dd) were above the normal ranges after the treatment, but these increases were exclusively attributable to one single patient who showed extremely high values of the mentioned 3 parameters after the treatment. In the other 11 patients all the parameters remained within normal ranges. The exceptional case was a 79-year-old woman with local recurrence; as shown in Table 2 she had markedly increased TAT-III, Dd and PIC at week 4 after the start of the treatment. However, the patient did not develop thromboembolism clinically and also the remaining 11 patients were free from clinical complications associated with the treatment.

Discussion. It has been reported that TAM may reduce AT-III levels (1–3), while MPA may increase AT-III and PC levels (1, 2). The increases of AT-III and PC caused by MPA do not seem to indicate a state of hypercoagulation (1, 2). It has been suggested that TAM-induced decrease of AT-III may play a role in the etiology of thromboembolism (3). It seems possible that the effects of TAM and MPA on the coagulation-fibrinolytic systems could cancel each other. In the present study of combined treatment with TAM and MPA both AT-III and PC remained within normal range. A shortening of APTT has been reported after therapy with MPA alone (1), but in the present study the mean value of APTT remained within the normal range after the combined use of MPA and TAM. In 11 of our 12 patients all the examined parameters were within the normal range after 4 weeks of TAM and MPA treatment. In one exceptional case a 79-year-old woman, TAT-III, Dd and PIC were considerably increased after 4 weeks. It may be postulated that in this patient generation of thrombin, formation of cross-linked fibrin and increased fibrinolysis occurred simulataneously, leading to the formation of microthrombi, which were dissolved without clinical signs. The changes of these parameters could all be secondary to the formation of microthrombi. Shortening of APTT during MPA, decrease of AT-III during TAM and simultaneous increases of TAT-III, Dd and PIC during treatment with these drugs should be carefully monitored. The rationale of combined TAM and MPA therapy has been confirmed by experimental and clinical studies (9, 10). This combination might be worthy of further studies from the viewpoint of reducing the risk of thrombotic complications in breast cancer patients.

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